HEPATITIS C UPDATE

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I , Antonio Sanchez, MD, disclose the following financial relationship(s) with manufacturers of health care products:

Grant/Research Support: Merck, Ocera, Gilead

I, Antonio Sanchez, MD will not discuss any medical devices during my presentation.

Learning Objectives

Overview of chronic hepatitis C

Review the evolution of treatment options

Discuss current approved hepatitis C treatment

Clinical Scenario

60 y/o Caucasian woman

Cirrhosis secondary to chronic hepatitis C

Genotype 1a, treatment naïve

Liver transplant - March 2013

Progressive cholestasis - GGT 500 - 700

Liver biopsy ➡ mild inflammation no fibrosis

Clinical Scenario

60-year-old woman , s/p LT in March 2013

No rejection, progressively elevated liver enzymes

Admitted in December 2013

Worsening jaundice (bilirubin of 8 mg/dl), hepatic encephalopathy, acute kidney injury (GFR of 8ml/min, requiring hemodialysis), and respiratory failure.

TREATMENT

OPTIONS ?

HCV: Background

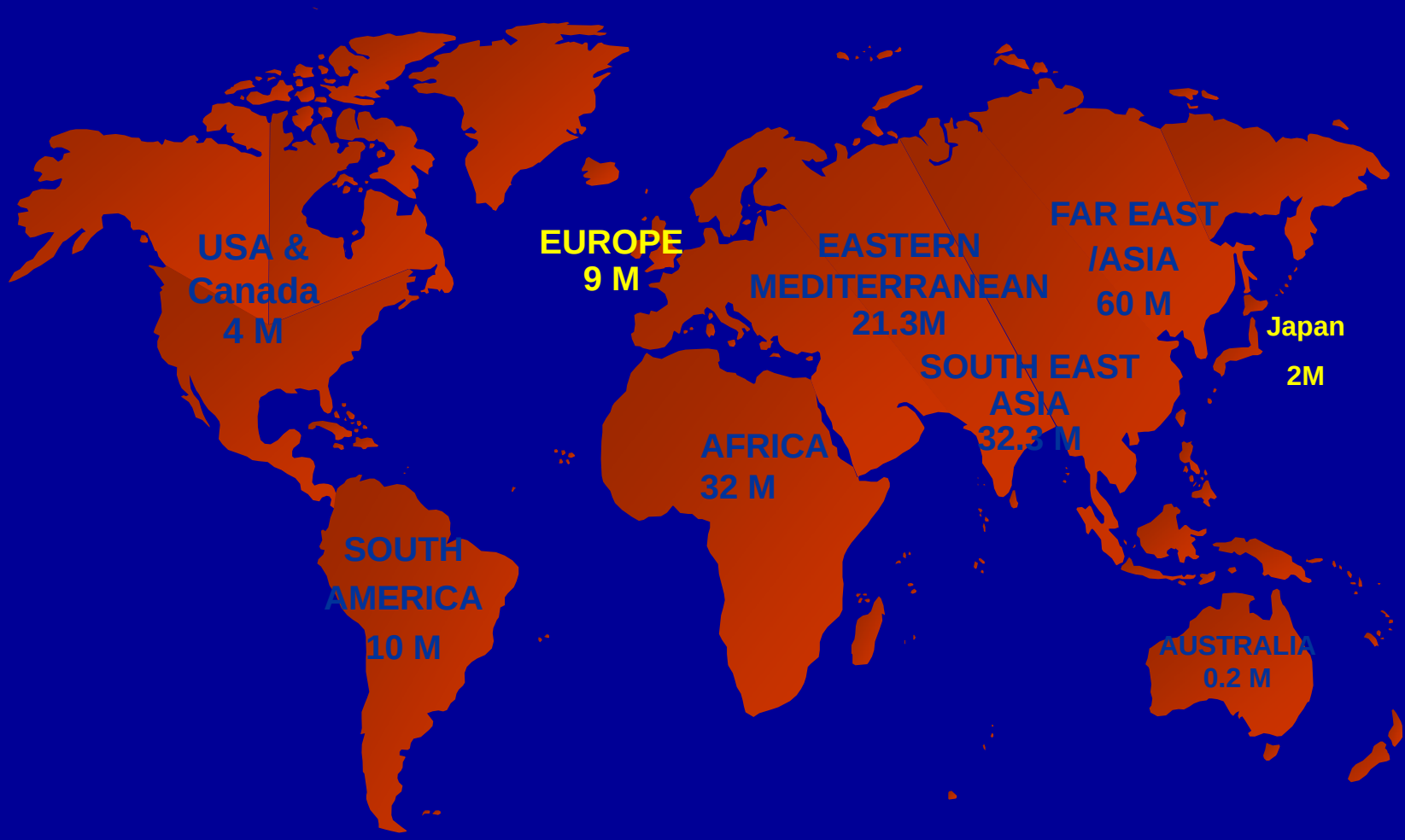
1-2% US population infected: 3 - 4 million

More prevalent than HIV

Men >Women -Patients not aware of infection

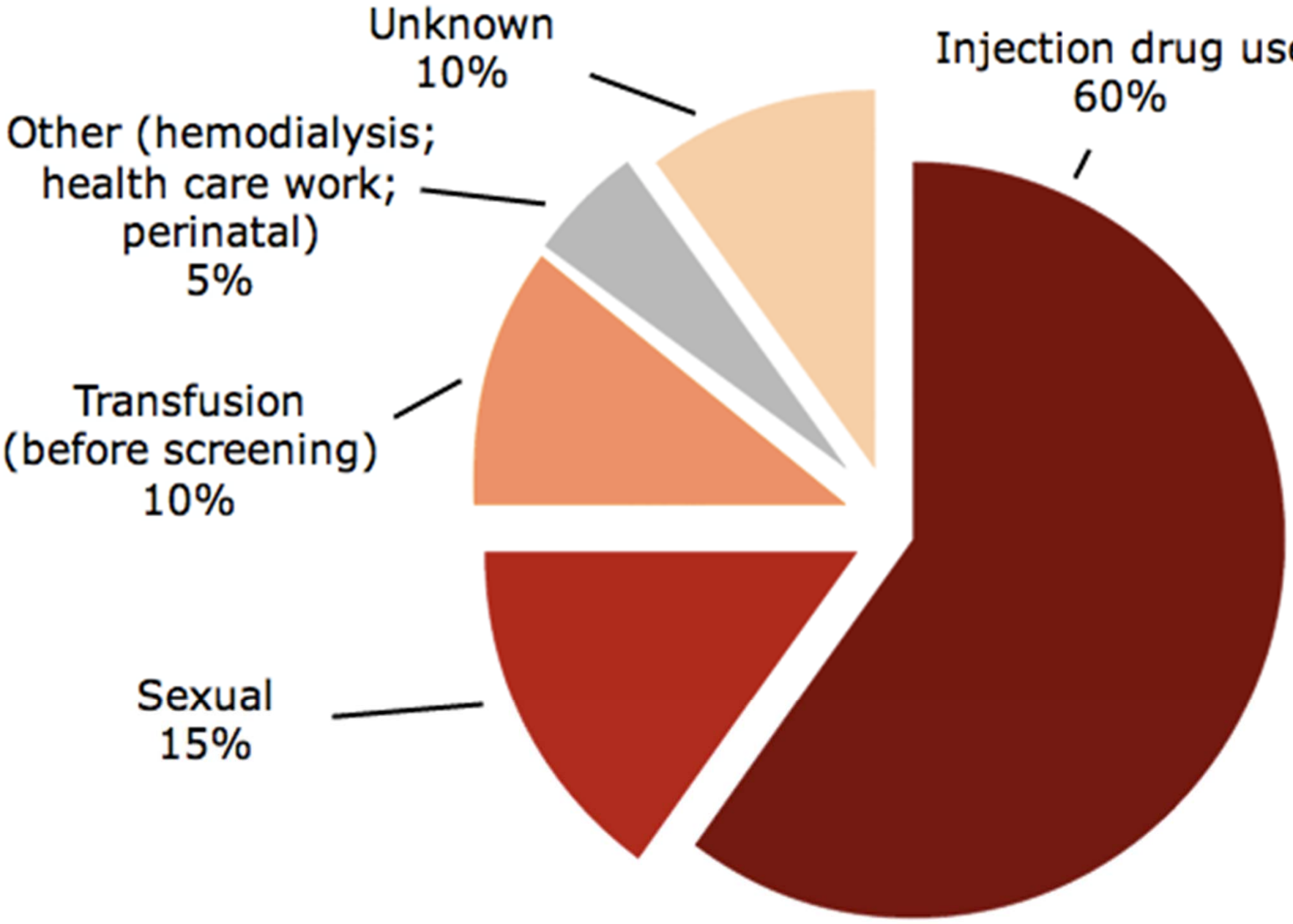
Inversely proportional to socioeconomic status

HCV worldwide

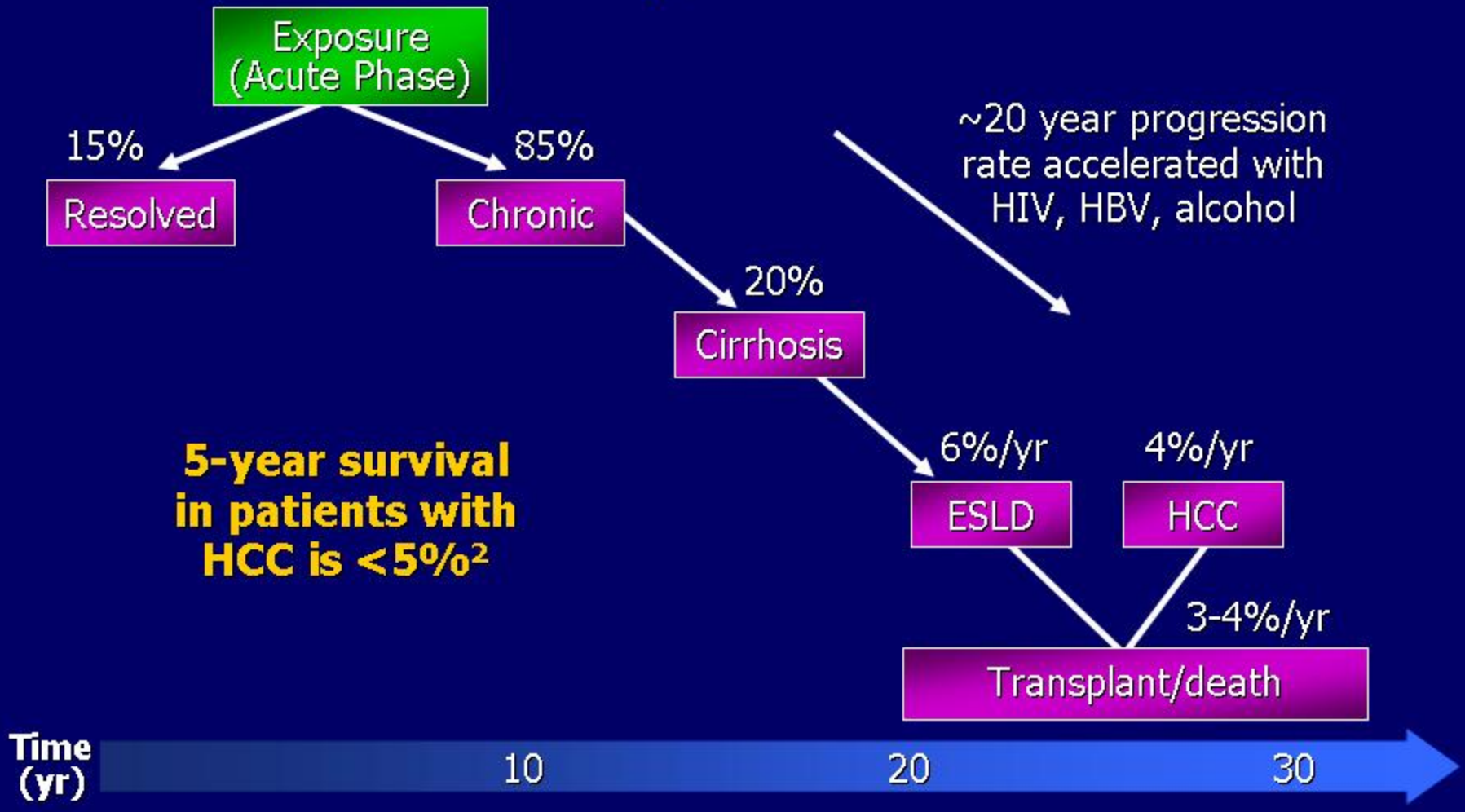


170 Millions worldwide

WHO, 1999


Unknown
10%
Injection drug use
60%
Other (hemodialysis;
health care work;
perinatal)
5%
Transfusion
(before screening)
10%
Sexual
15%

Natural History of HCV Infection



HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

DiBisceglie et al. *Hepatology*. 2000;31(4):1014-1018.

TABLE 1

Screening Recommendations for Hepatitis C Virus

CDC	AASLD	USPSTF	NIH
Born in the United States between 1945 and 1965	Persons who have injected illicit drugs, including those who injected only once and do not consider themselves to be drug users.	Born in the United States between 1945 and 1965	Same as CDC
Any injection of illegal drugs	HIV infection	Past or current injection-drug use	Received a blood transfusion or organ transplant before 1992
Received clotting factors made before 1987	Hemophiliac who received clotting factor concentrates before 1987	Received a blood transfusion before 1992	Has had multiple sexual partners
Received blood/organs before July 1992	Hemodialysis	Long-term hemodialysis	Has spouse or household contacts who is infected with HIV
Had been on chronic hemodialysis	Unexplained abnormal aminotransferase levels	Born to a mother infected with HCV	Shared instruments for intranasal cocaine use
Have evidence of liver disease	Recipients of transfusions or organ transplants before July 1992	Incarceration	Incarceration
infected with HIV	Children born to mothers infected with HCV	Intranasal drug use	
Healthcare workers after needle stick, sharps, mucosal exposure to HCV-positive blood	Healthcare, emergency medical, and public safety workers who experience a needle-stick injury or mucosal exposure to HCV-positive blood	Received an unregulated tattoo	
Children born to HCV-positive women	Current sexual partners of individuals infected with HCV	Other percutaneous exposures	

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CDC, Centers for Disease Control and Prevention; NIH, National Institutes of Health; USPSTF, U.S. Preventive Services Task Force

Sources: Ref 1-4

Goals of Hepatitis C Treatment

Eradicate hepatitis C virus (predicted by SVR)

Prevent complications of liver disease

Delay disease progression

Prevent recurrence after liver transplant

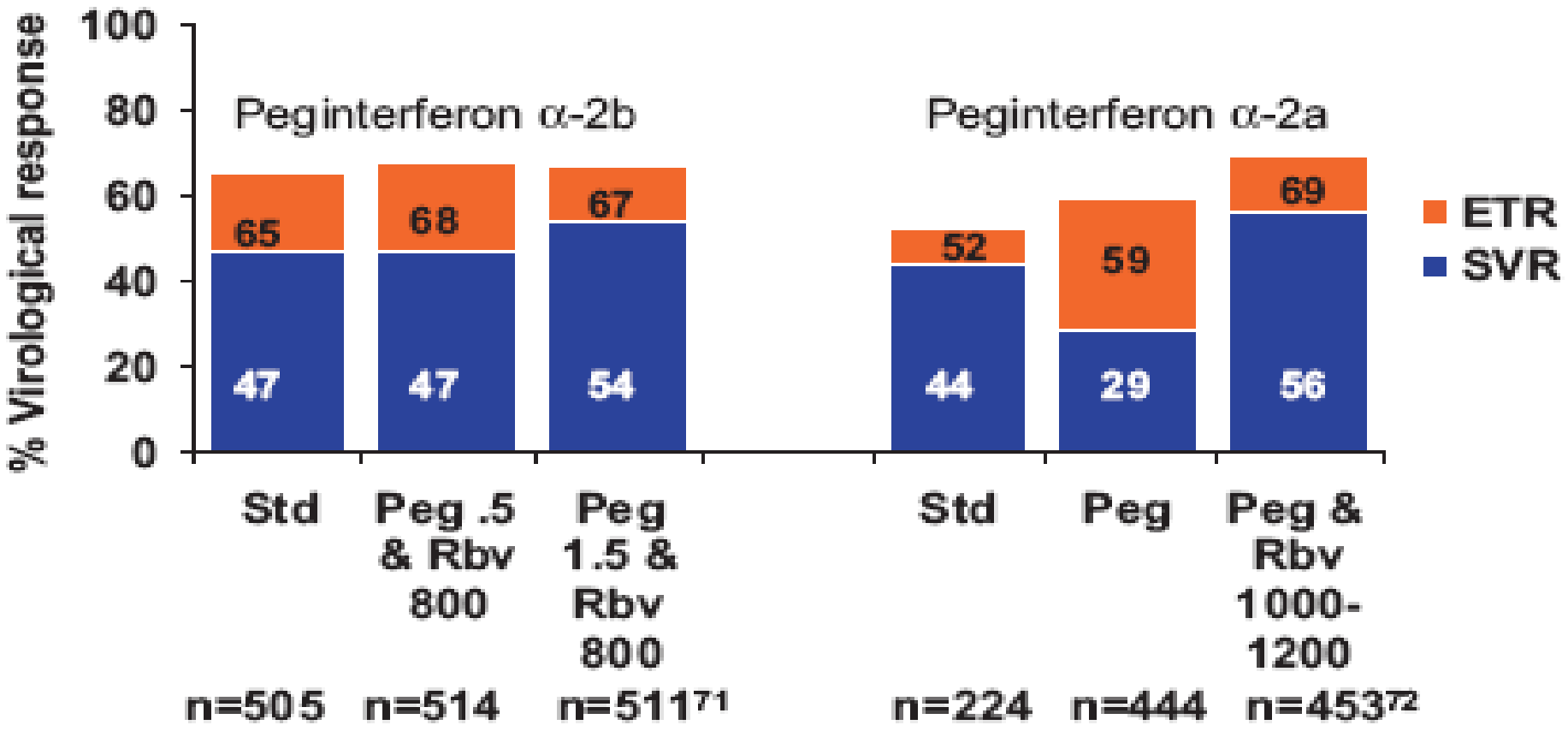


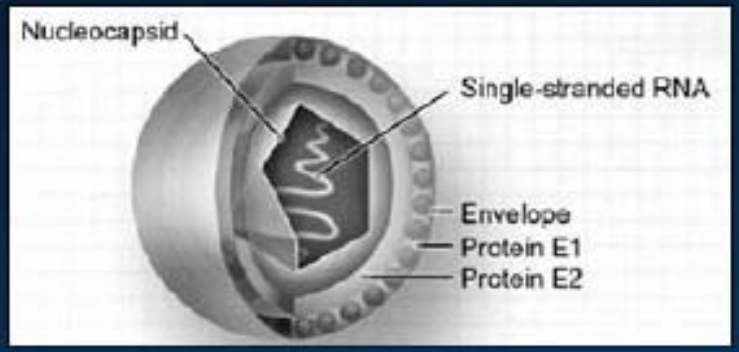
Fig. 2. Virological responses to pegylated interferon and ribavirin in the two U.S. Registration trials.[71,72] ETR, end-of-treatment response; SVR, sustained virological response.

Ghany, MG, Strader, DB, Thomas, DL, Seeff, LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49:1335.

Predictors of Virologic Response

Viral Factors

- Genotype
- Viral Load



Social Factors

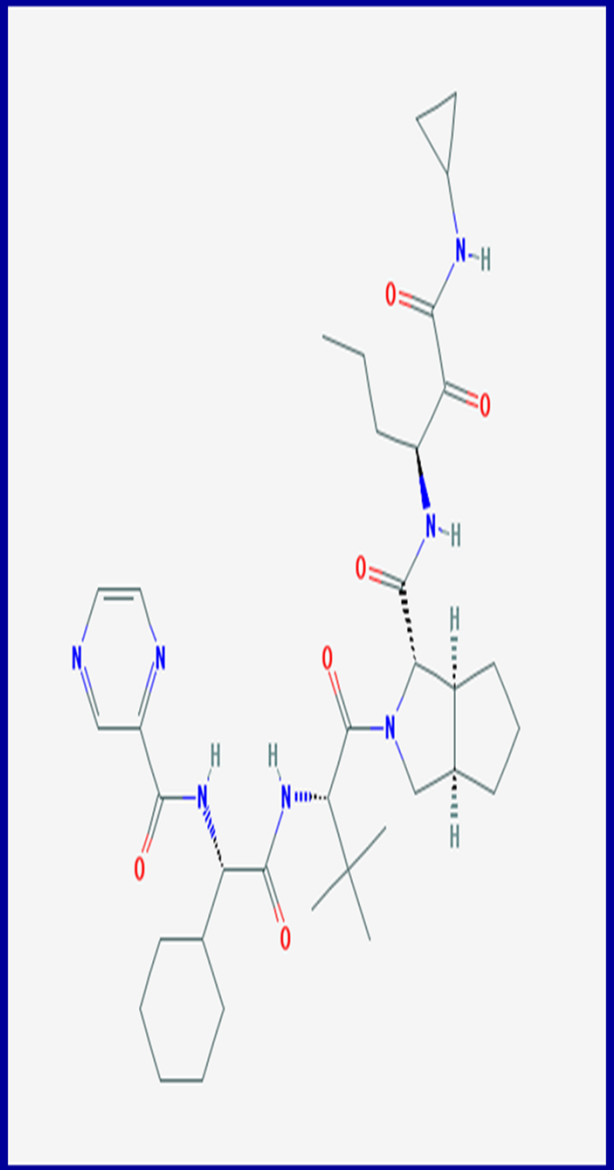
- Adherence
- Mental health issues
- Substance use

Host Factors

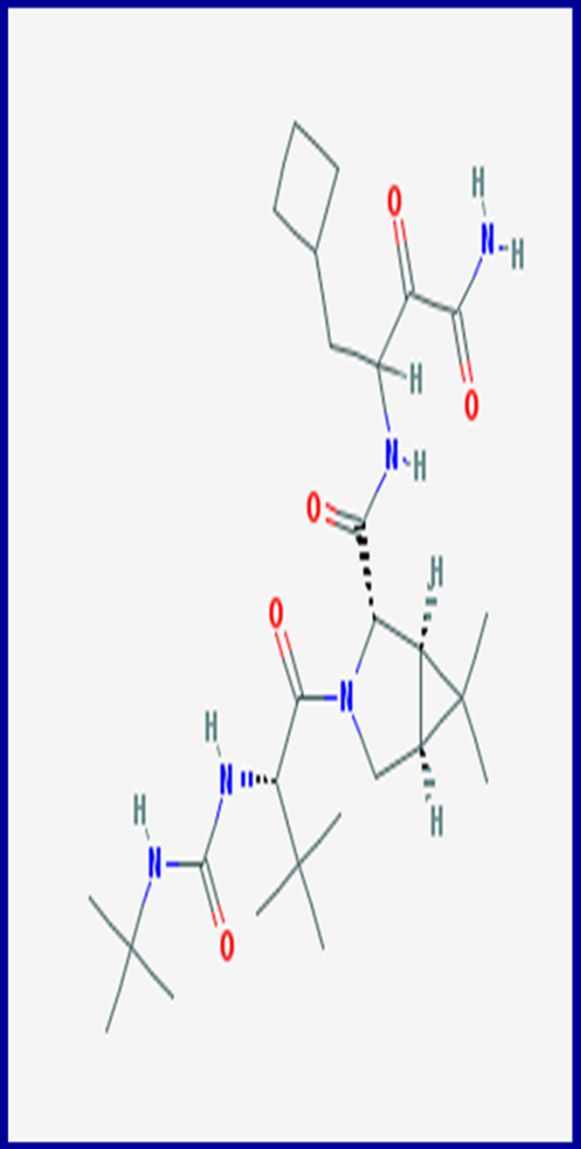
- Age
- Cirrhosis
- Coinfection (HIV, HBV)
- Gender
- Hepatic Fe Overload
- Hyperinsulinemia
- Race
- Steatosis
- Weight

Ferenci P. *Semin Liver Dis*. 2004;24:25-31.
NIH Consensus Development Conference Statement. *Gastroenterology*. 2002;123:2082-2099.

Telaprevir

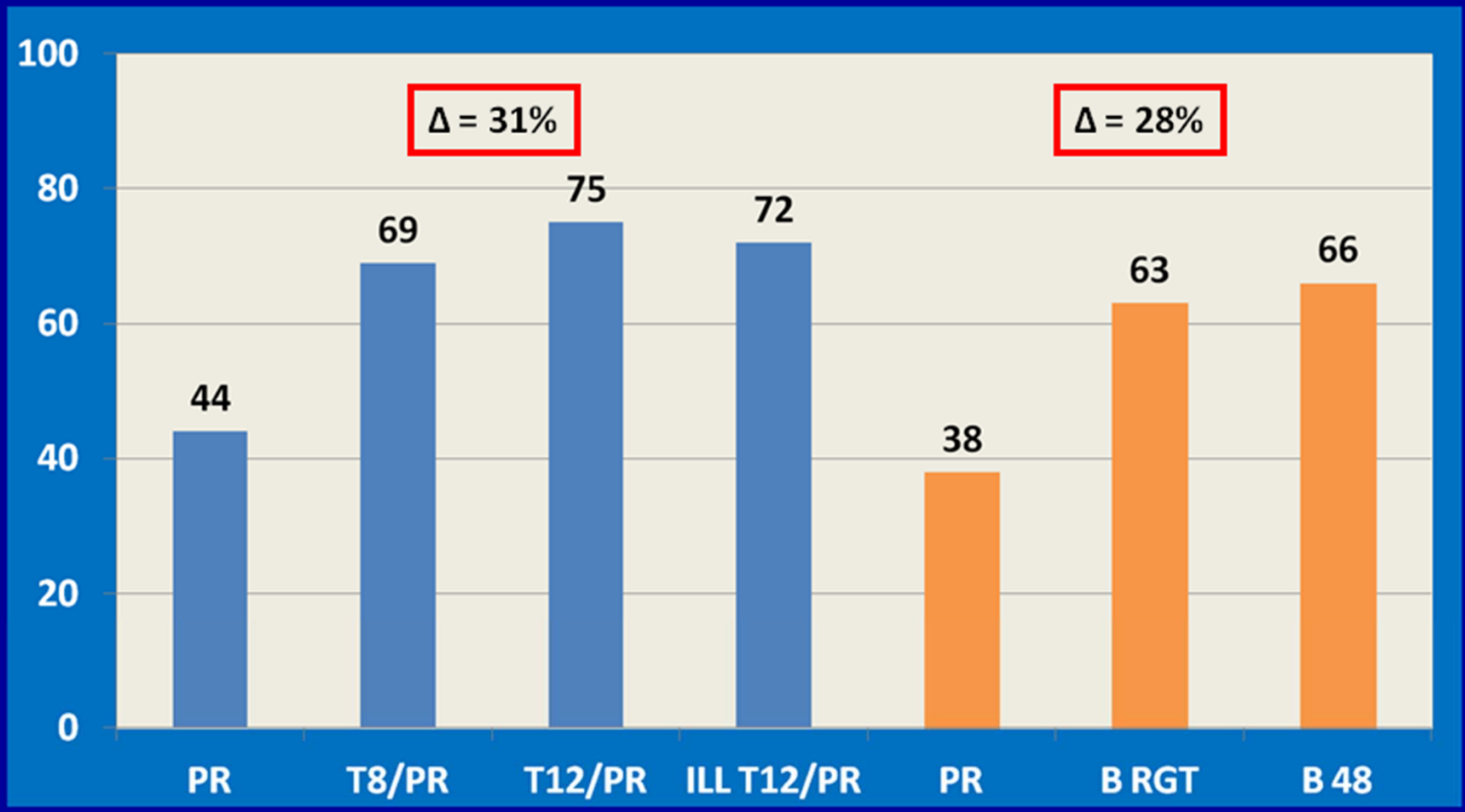


Boceprevir

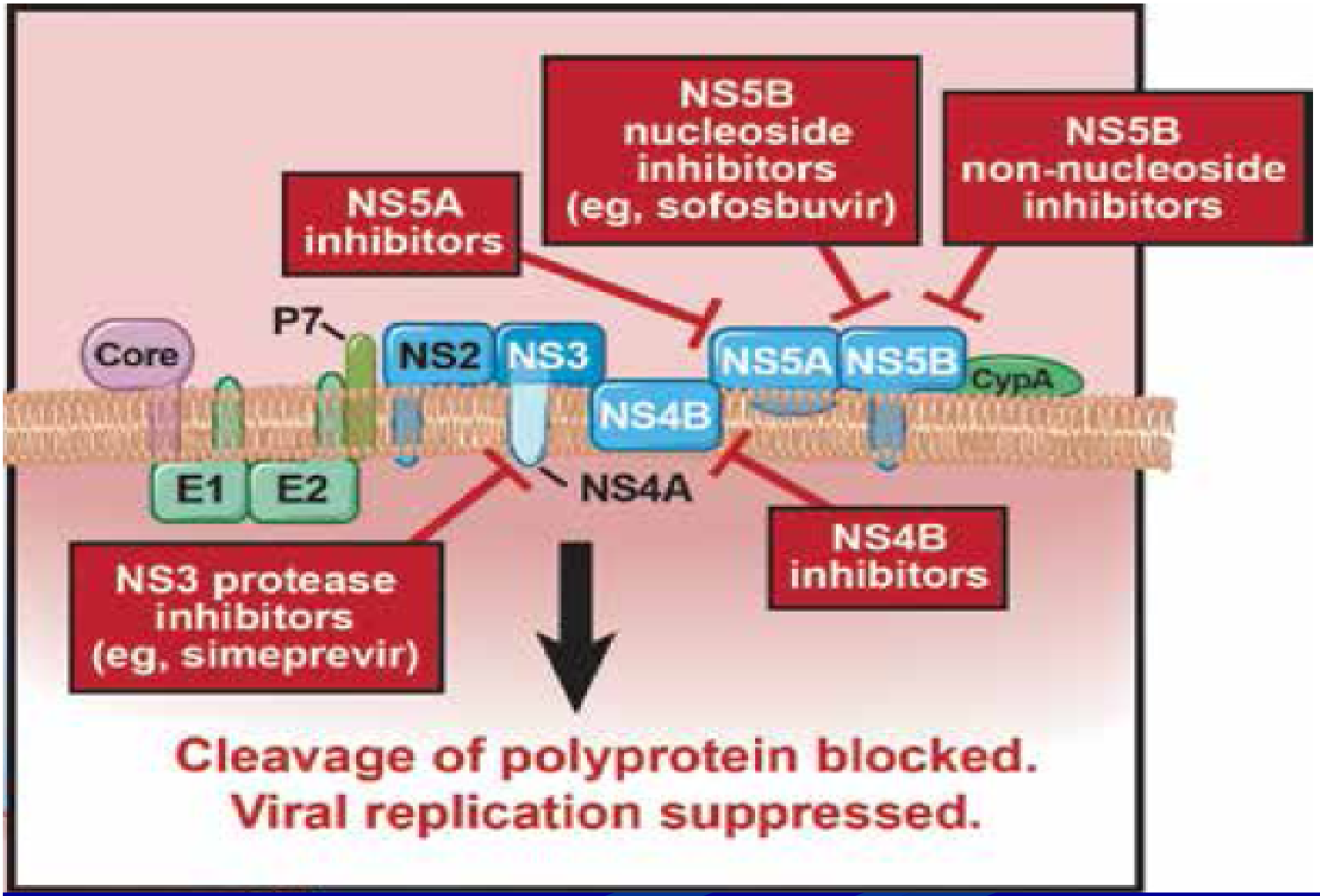


SVR in Treatment Naïve Patients

From ADVANCE, ILLUMINATE (ILL), and SPRINT-2

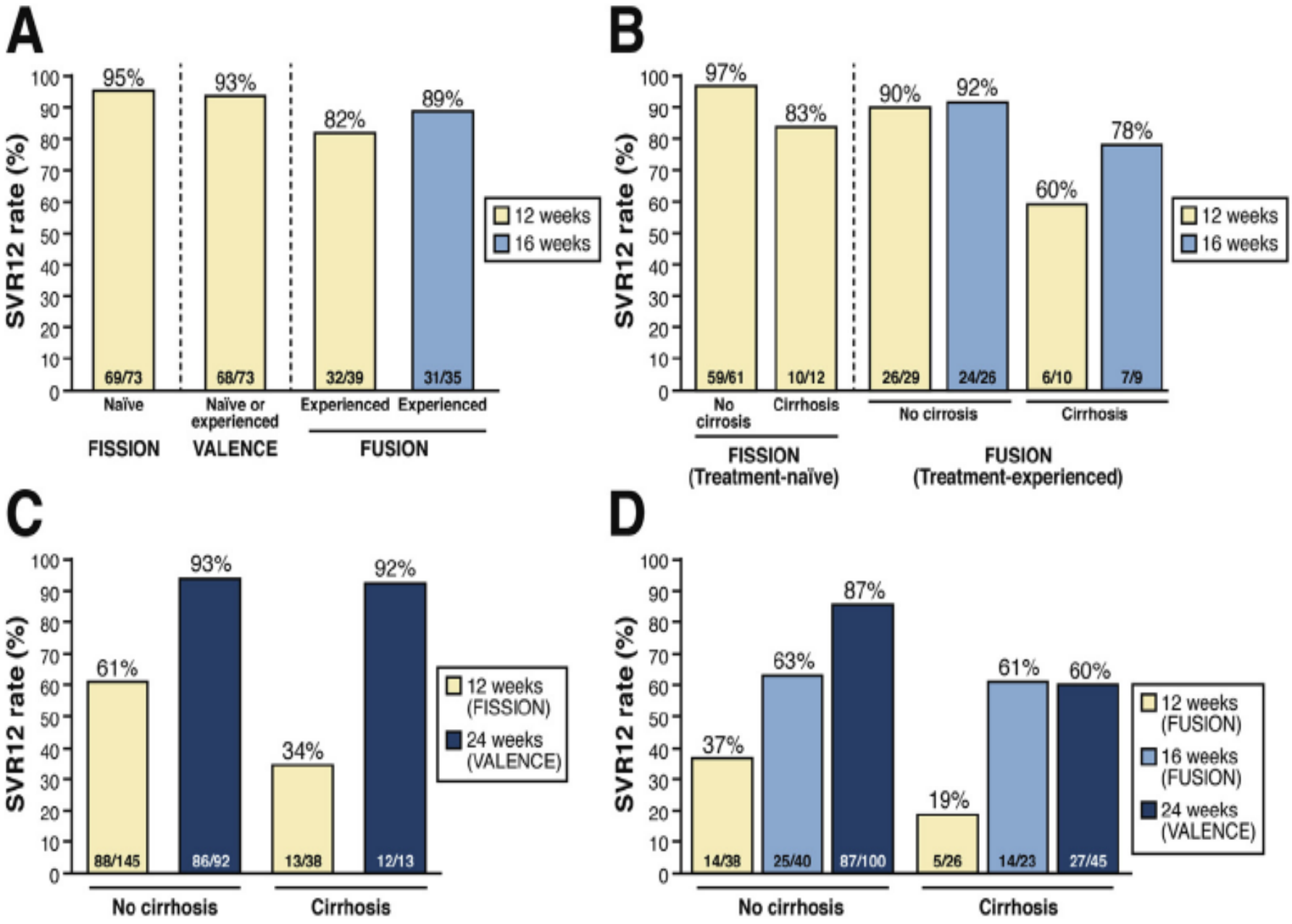


ADVANCE. N Engl J Med 2011;364:2405-2416. ILLUMINATE. N Engl J Med 2011;365:1014-1024. SPRINT-2. N Engl J Med 2011;364:1195-1206.


NS5B
nucleoside
inhibitors
(eg, sofosbuvir)
NS5B
non-nucleoside
inhibitors
NS5A
inhibitors
P7
Core
NS2
NS3
NS5A
NS5B
CypA
NS4B
E1
E2
NS4A
NS3 protease
inhibitors
(eg, simeprevir)
NS4B
inhibitors
Cleavage of polyprotein blocked.
Viral replication suppressed.

Sofosbuvir (SOF) (GS-7977)

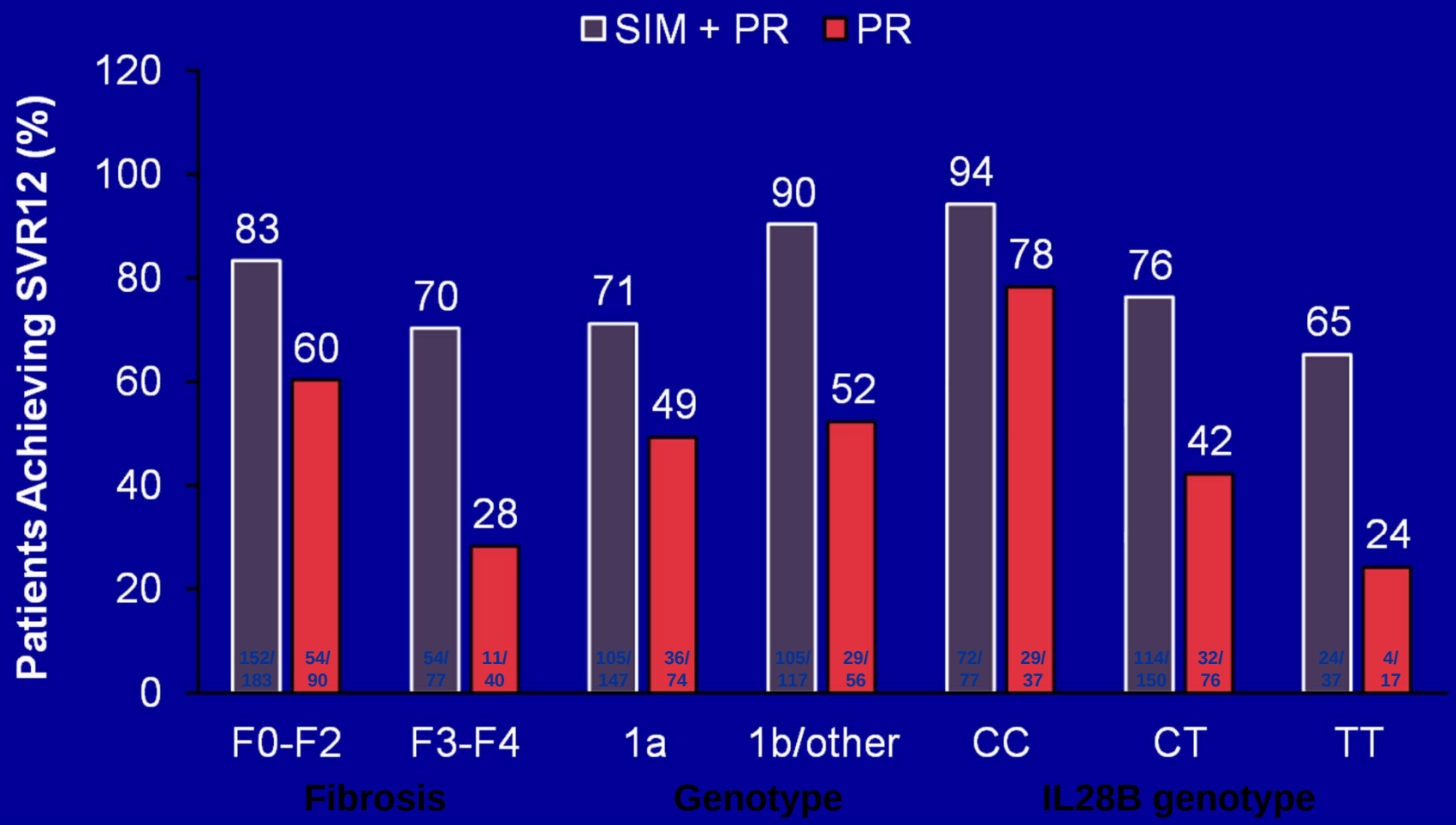
- NS5B nucleotide polymerase inhibitor
- Favorable administration profile
  - Once daily, no food effect
  - No drug-drug interactions


A
SVR12 rate (%)
95%
93%
82%
89%
69/73
68/73
32/39
31/35
Naïve
Naïve or experienced
Experienced
Experienced
FISSION
VALENCE
FUSION
12 weeks
16 weeks
B
SVR12 rate (%)
97%
83%
90%
92%
60%
78%
59/61
10/12
26/29
24/26
6/10
7/9
No cirrosis
Cirrhosis
No cirrosis
Cirrhosis
FISSION (Treatment-naïve)
FUSION (Treatment-experienced)
12 weeks
16 weeks
C
SVR12 rate (%)
61%
93%
34%
92%
88/145
86/92
13/38
12/13
No cirrhosis
Cirrhosis
12 weeks (FISSION)
24 weeks (VALENCE)
D
SVR12 rate (%)
37%
63%
87%
19%
61%
60%
14/38
25/40
87/100
5/26
14/23
27/45
No cirrhosis
Cirrhosis
12 weeks (FUSION)
16 weeks (FUSION)
24 weeks (VALENCE)

Simeprevir (TMC 435)

- NS3/4A protease inhibitor
- Antiviral activity against GT 1, 2, 4, 5 and 6
- One capsule, once per day

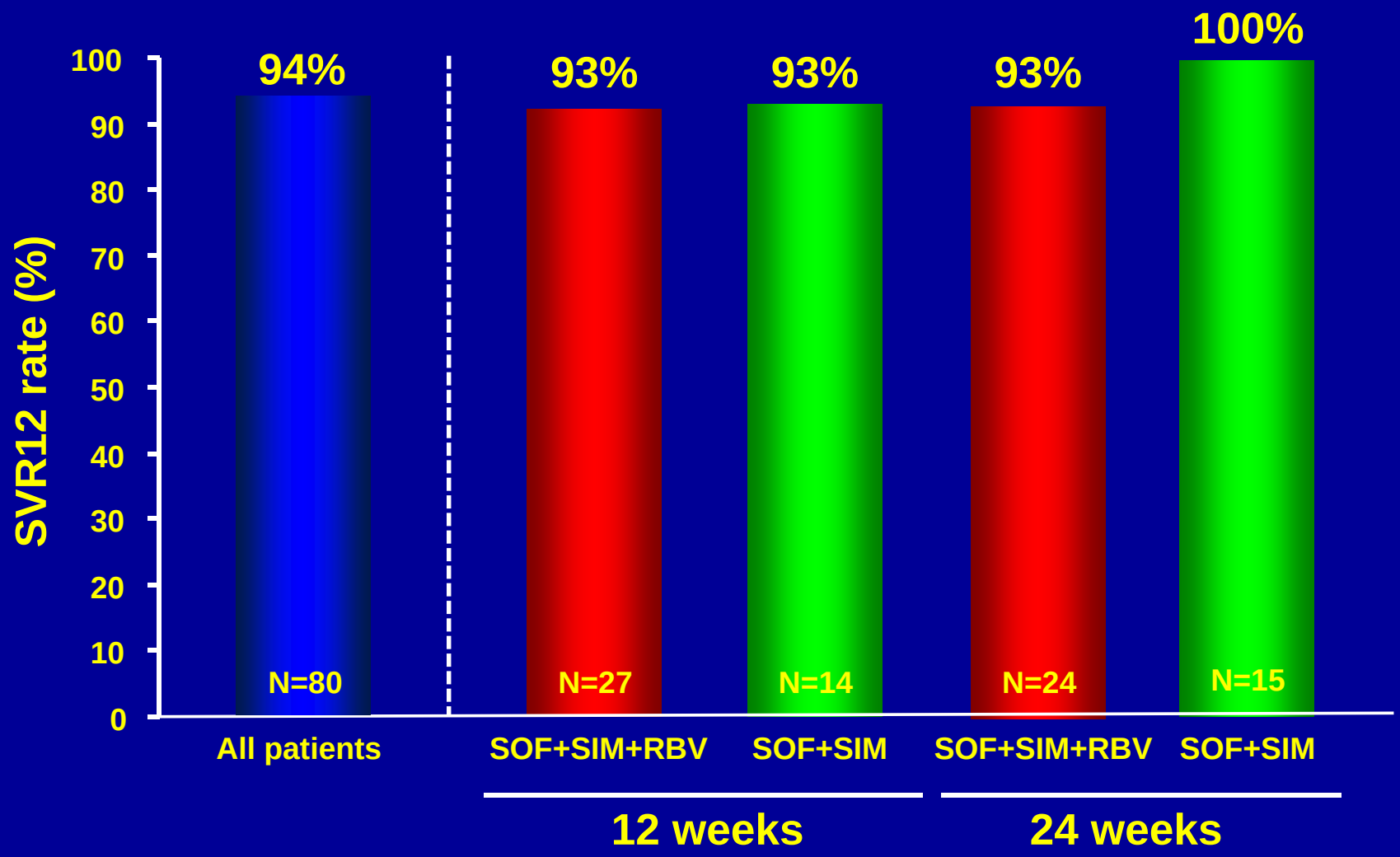
QUEST-1: SVR by Subgroup



I. Jacobson et al, Abstract 1425. EASL, April 2013

Sofosbuvir + Simeprevir ± RBV

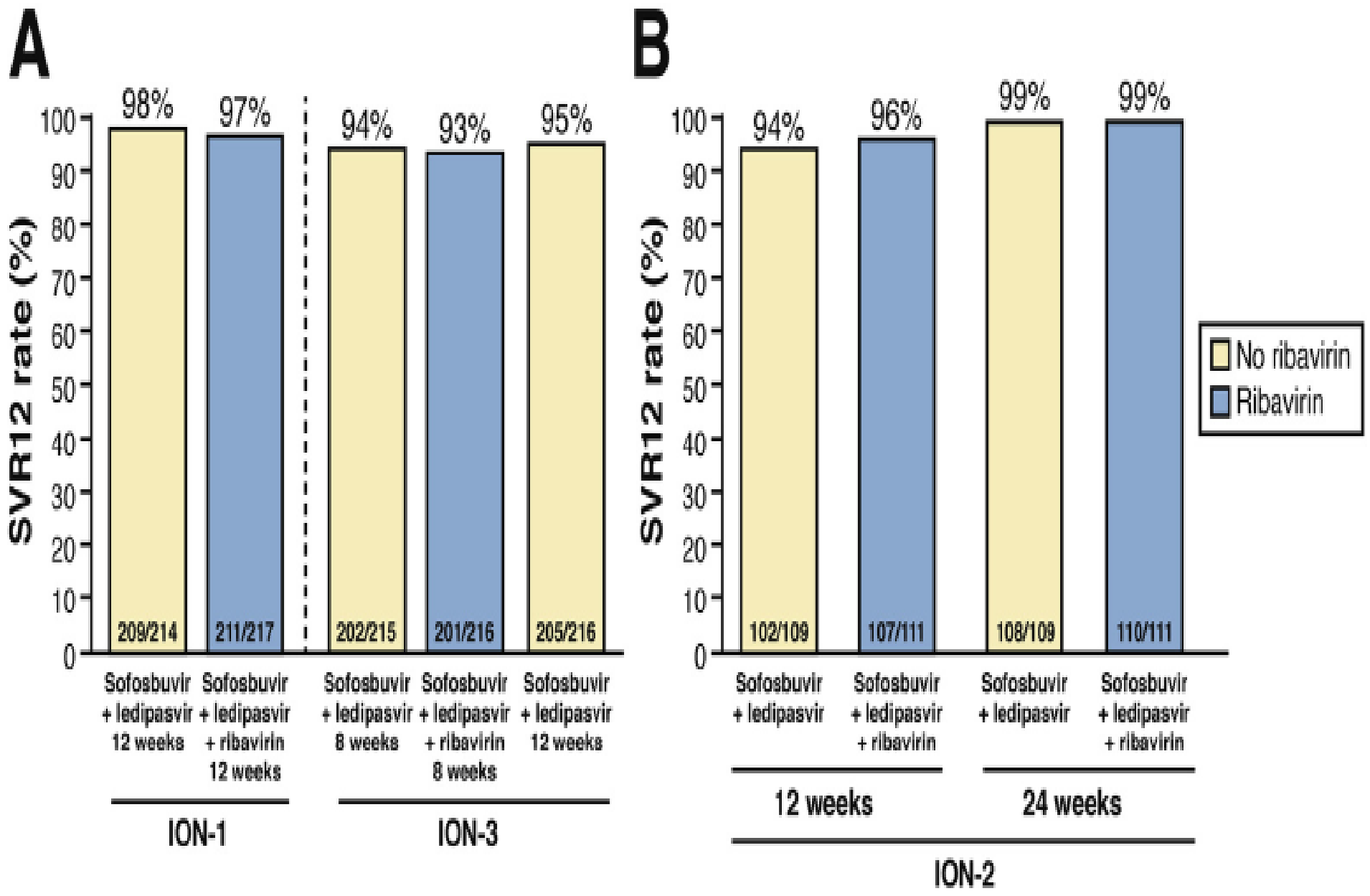
COSMOS Cohort 2- Gen 1, Naive and NR, F3-F4



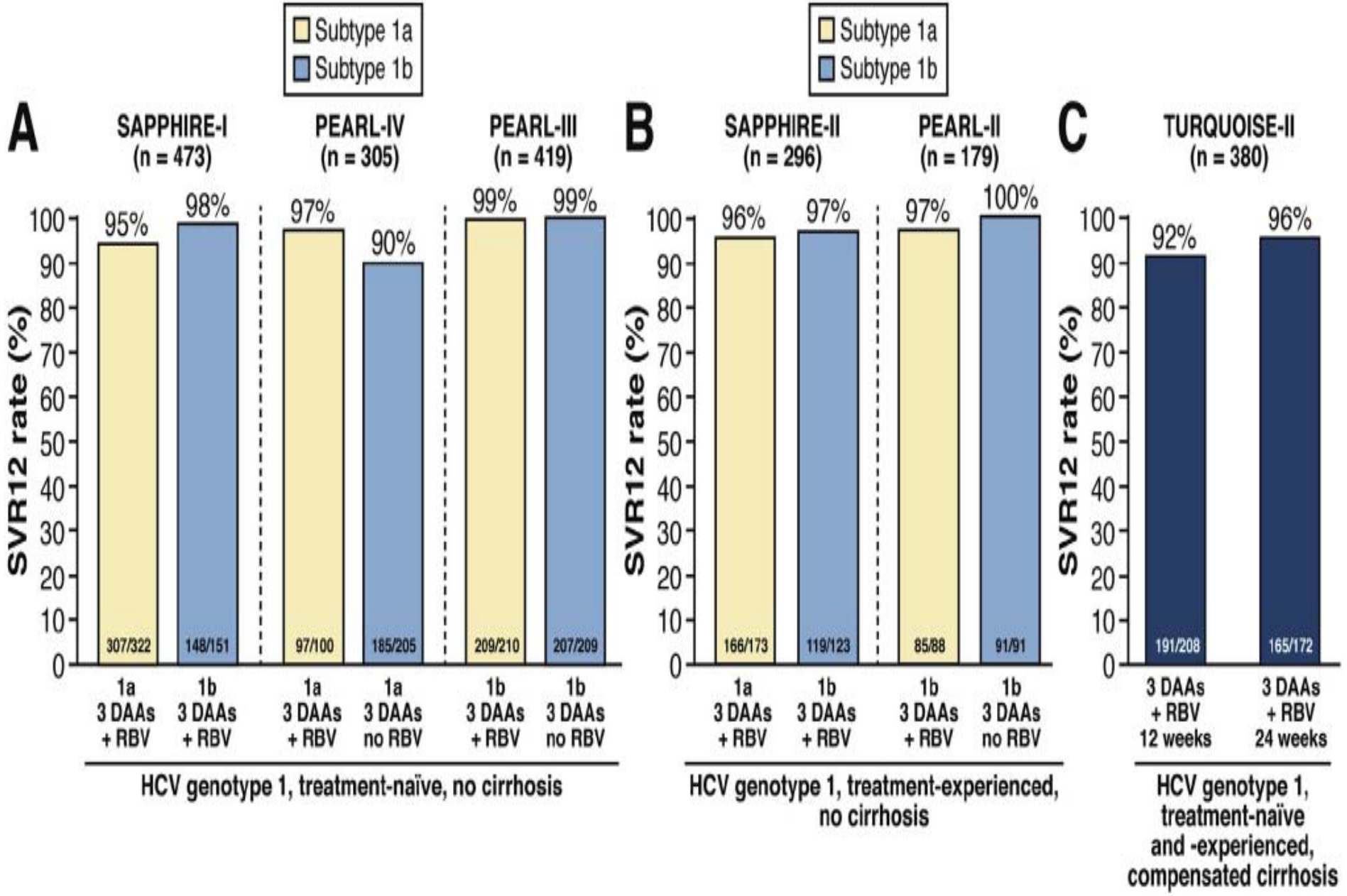
(Lawitz et al., Lancet 2014 Nov 15;384(9956):1756-65. *)*

- **Ledipasvir**
  - **Once-daily, oral, 90-mg**
    NS5A inhibitor
- **Sofosbuvir**
  - **Once-daily, oral, 400-mg**
    NS5B inhibitor
- **Sofosbuvir/Ledipasvir (HARVONI)**
  - **Once-daily, oral, fixed-dose (90/400 mg) combination tablet**
  - **Single-tablet regimen for hepatitis C**

FDC, fixed-dose combination.

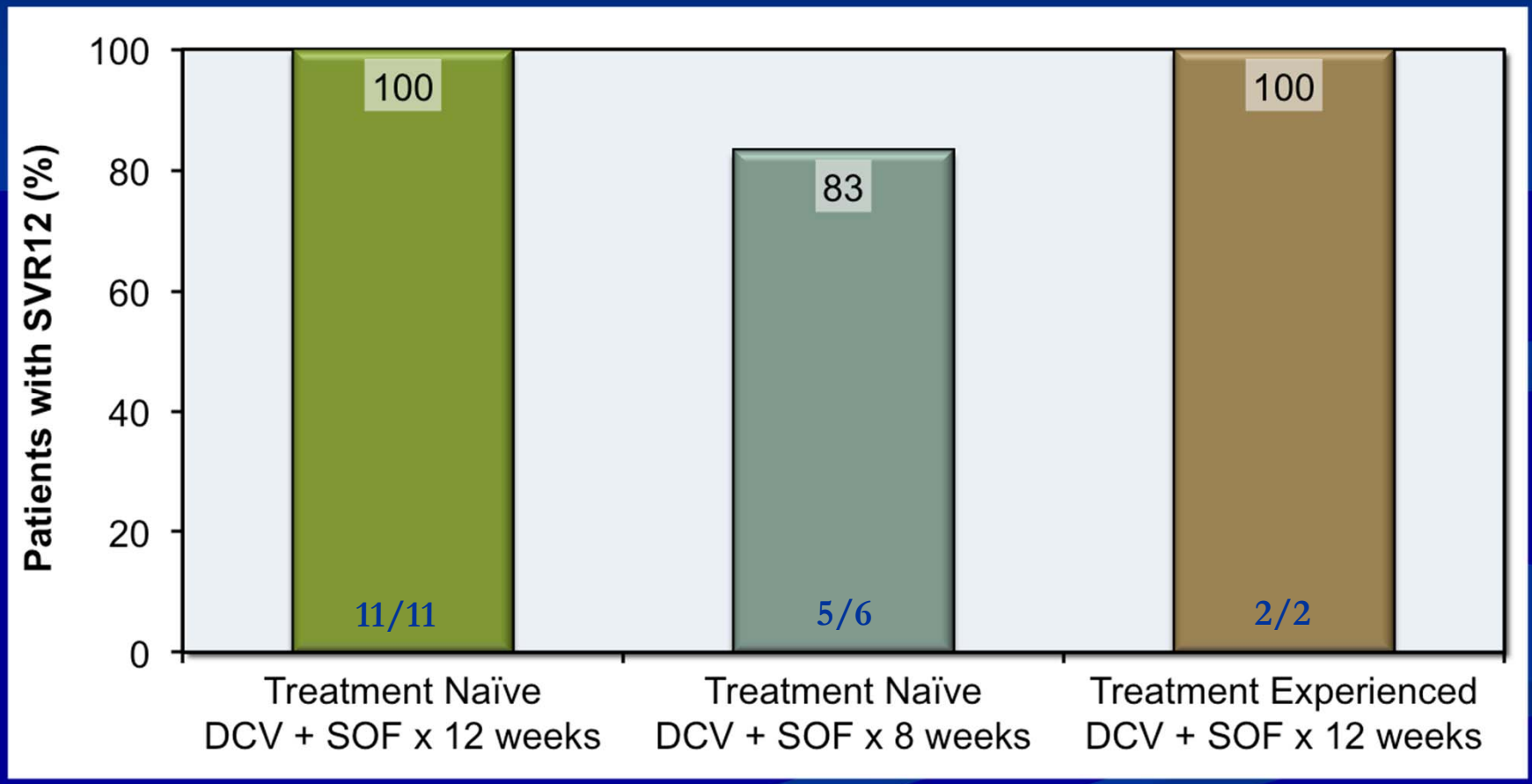

A
B
SVR12 rate (%)
100
90
80
70
60
50
40
30
20
10
0
98%
97%
94%
93%
95%
209/214
211/217
202/215
201/216
205/216
Sofosbuvir + ledipasvir 12 weeks
Sofosbuvir + ledipasvir + ribavirin 12 weeks
Sofosbuvir + ledipasvir 8 weeks
Sofosbuvir + ledipasvir + ribavirin 8 weeks
Sofosbuvir + ledipasvir 12 weeks
ION-1
ION-3
94%
96%
99%
99%
102/109
107/111
108/109
110/111
Sofosbuvir + ledipasvir
Sofosbuvir + ledipasvir + ribavirin
Sofosbuvir + ledipasvir
Sofosbuvir + ledipasvir + ribavirin
12 weeks
24 weeks
ION-2
No ribavirin
Ribavirin


viekira pak™
ombitasvir, paritaprevir and
ritonavir tablets; dasabuvir tablets


Subtype 1a
Subtype 1b
A
SAPPHIRE-I
(n = 473)
PEARL-IV
(n = 305)
PEARL-III
(n = 419)
SVR12 rate (%)
95%
98%
97%
90%
99%
99%
307/322
148/151
97/100
185/205
209/210
207/209
1a 3 DAAs + RBV
1b 3 DAAs + RBV
1a 3 DAAs + RBV
1a 3 DAAs no RBV
1b 3 DAAs + RBV
1b 3 DAAs no RBV
HCV genotype 1, treatment-naïve, no cirrhosis
Subtype 1a
Subtype 1b
B
SAPPHIRE-II
(n = 296)
PEARL-II
(n = 179)
SVR12 rate (%)
96%
97%
97%
100%
166/173
119/123
85/88
91/91
1a 3 DAAs + RBV
1b 3 DAAs + RBV
1b 3 DAAs + RBV
1b 3 DAAs no RBV
HCV genotype 1, treatment-experienced, no cirrhosis
C
TURQUOISE-II
(n = 380)
SVR12 rate (%)
92%
96%
191/208
165/172
3 DAAs + RBV 12 weeks
3 DAAs + RBV 24 weeks
HCV genotype 1, treatment-naïve and -experienced, compensated cirrhosis

Daclatasvir + Sofosbuvir
ALLY-2 Trial: Results for Genotype 2

SVR12, Genotype 2

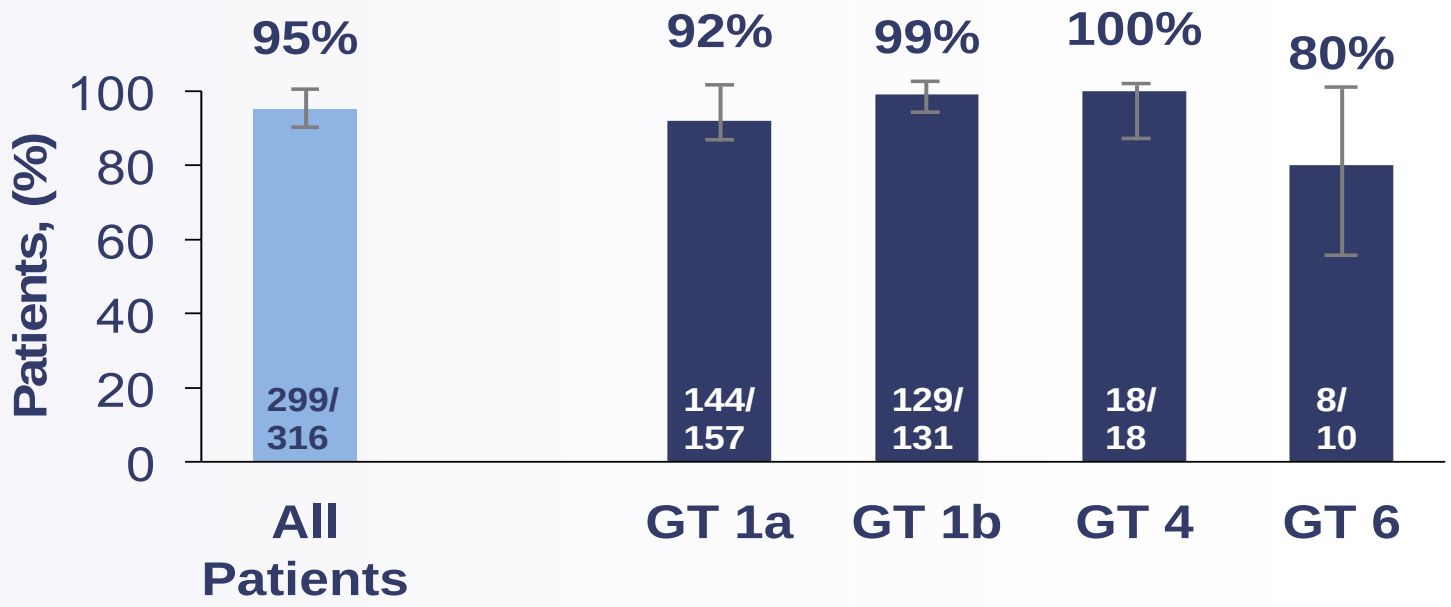


Abbreviations: DCV = daclatasvir; SOF = sofosbuvir

Wyles DL, et al. N Engl J Med. 2015;373:714-25.

MK-5172 + MK- 8742

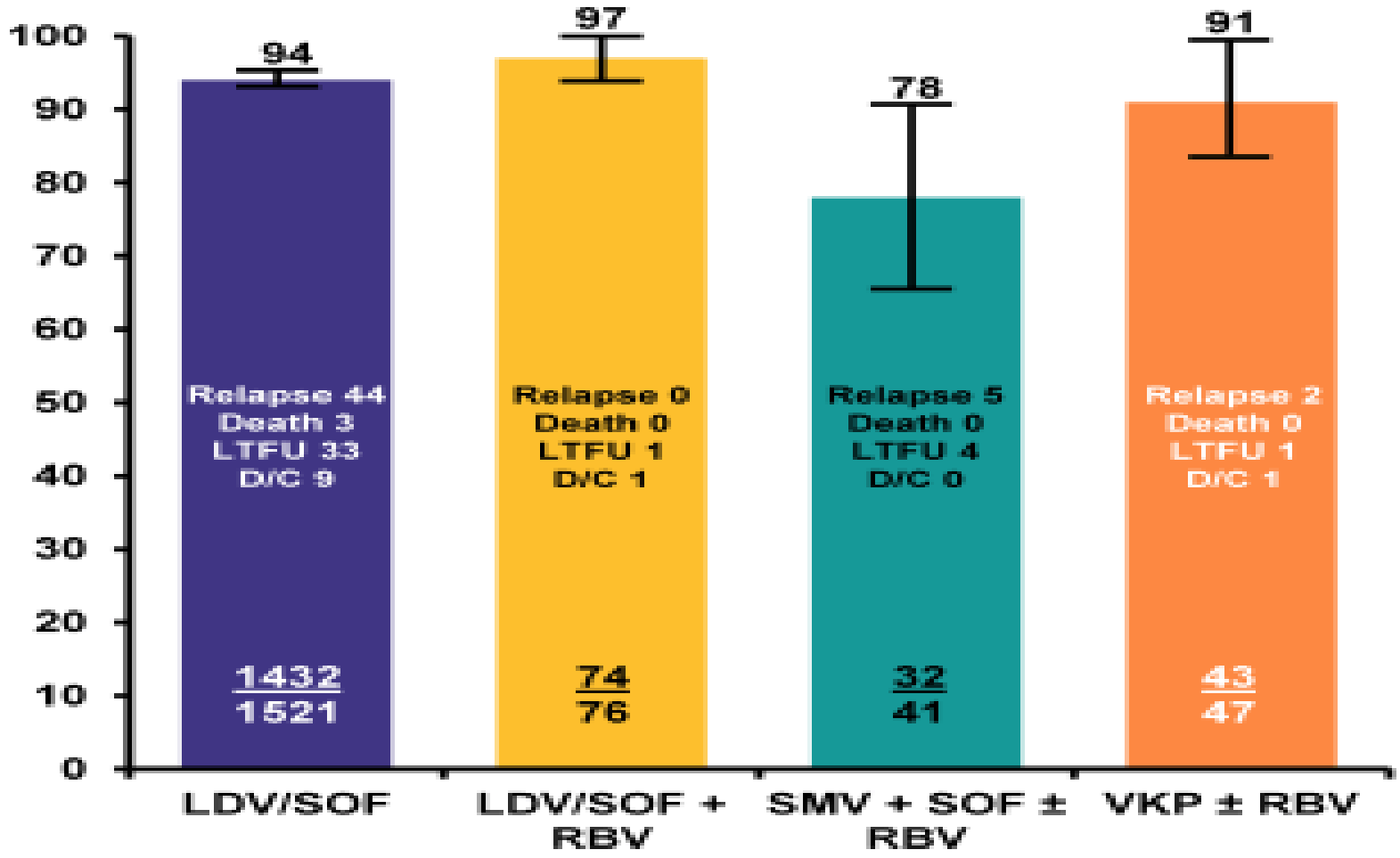
SVR 12: Full Analysis Set



Non-virologic failure	4		3	1	0	0
Breakthrough	1		1	0	0	0
Relapse	12		9	1	0	2

Zeuzem et al., Abstract #G07, EASL 2015

REAL LIFE – HEPATITIS C TREATMENT - TRIO NETWORK



SPECIAL POPULATIONS

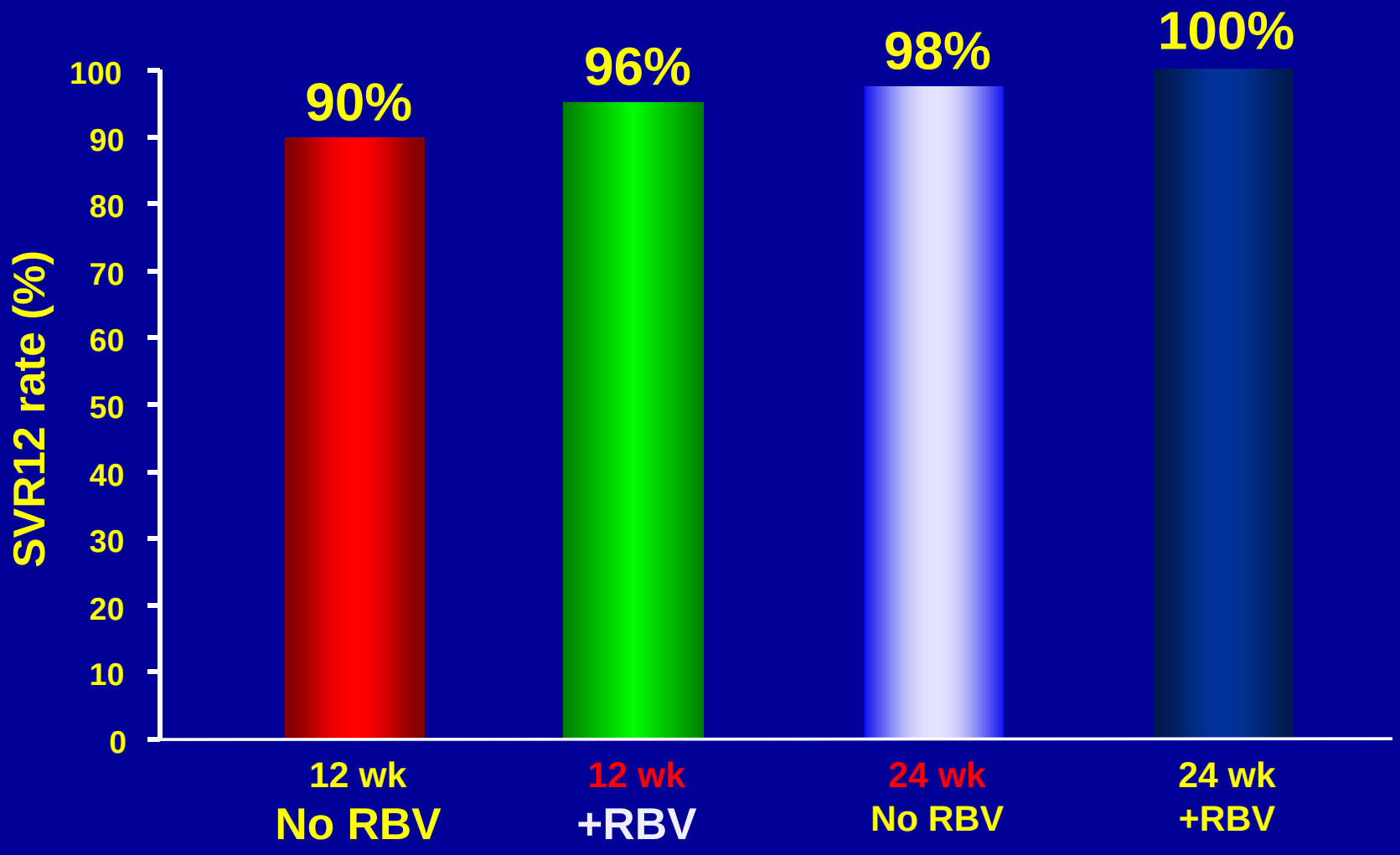
Decompensated Cirrhosis

Author	N	Rx	RNA Negative EOT	RNA Negative SVR
Iacobellis	66	PEG/RBV	49%	20%
Forns	51	PEG/RBV	29%	20%
Tekin	20	PEG/RBV	45%	30%
Annicchiarico	15	PEG/RBV	47%	20%
Everson	124	IFN/RBV	46%	24%
Forns	30	IFN/RBV	30%	20%
Thomas	20	IFN	60%	20%
Amarapurkar	18	IFN±RBV	61%	38%
Crippin	15	IFN±RBV	33%	0%
Totals	359		44%	24%

Martinez-Camacho A, Fortune BE, Everson GT. Treating HCV Prior to Liver Transplantation. In *Chronic Hepatitis C: Advances in Treatment, Promise for the Future.* ML Shiffman (ed). 2012. Springer Science-Business. NY.

Sofosbuvir/Ledipasvir ± RBV

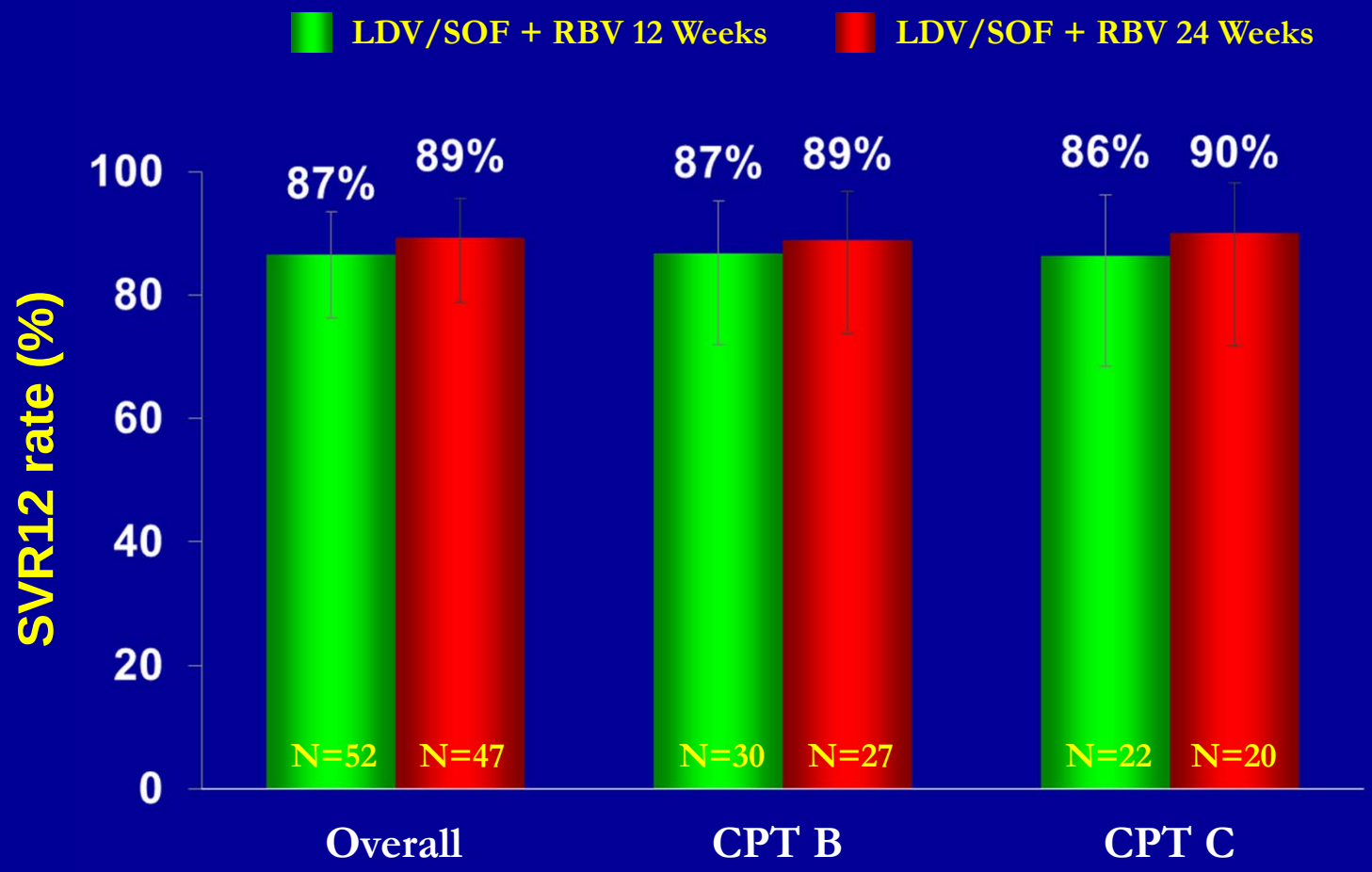
Gen 1 Rx-experienced patients with compensated cirrhosis



(Bourlière et al., AASLD 2014)

Sofosbuvir/Ledipasvir + RBV

Genotype 1,4 decompensated cirrhosis

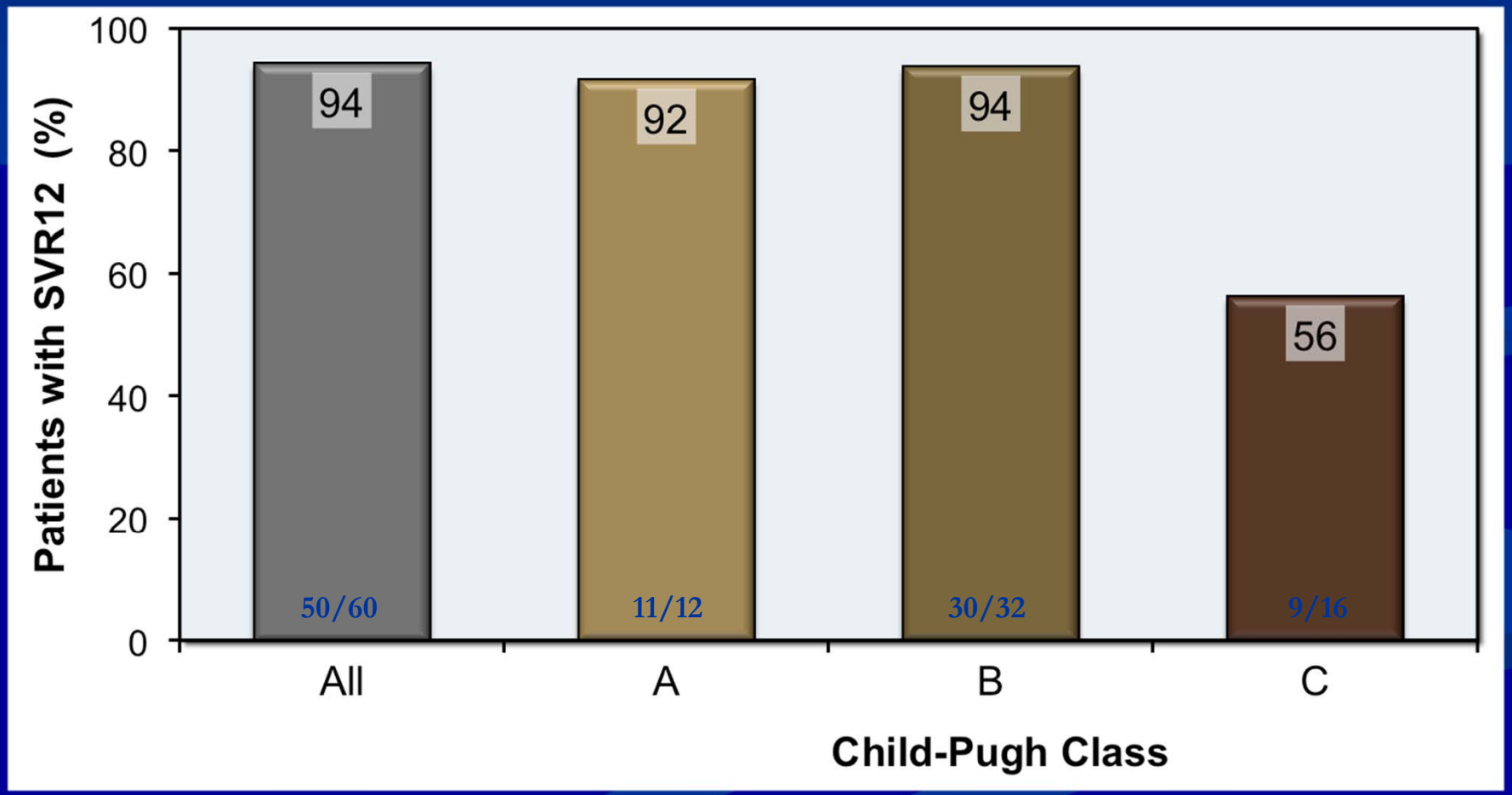


- Source: Flamm SL, al. 65th AASLD. 2014: Abstract 239.

DCV + SOF + RBV in Decompensated Cirrhosis

ALLY-1: Results for Advanced Cirrhosis Cohort

ALLY-1: SVR12 Results for Advanced Cirrhosis Cohort by Child-Pugh Class



Poordad F, et al. Hepatology. 2016 January 11

Hepatitis C and Liver Transplantation

Hepatitis C → indication for liver transplant

Virologic recurrence following LT is universal

30% of HCV-infected recipients develop cirrhosis from hep C recurrence by 5th postop year

Proportion increasing with duration of follow-up

Agressive recurrence – fibrosing cholestatic HCV

Table 3
Preemptive anti–hepatitis C virus therapy after liver transplantation

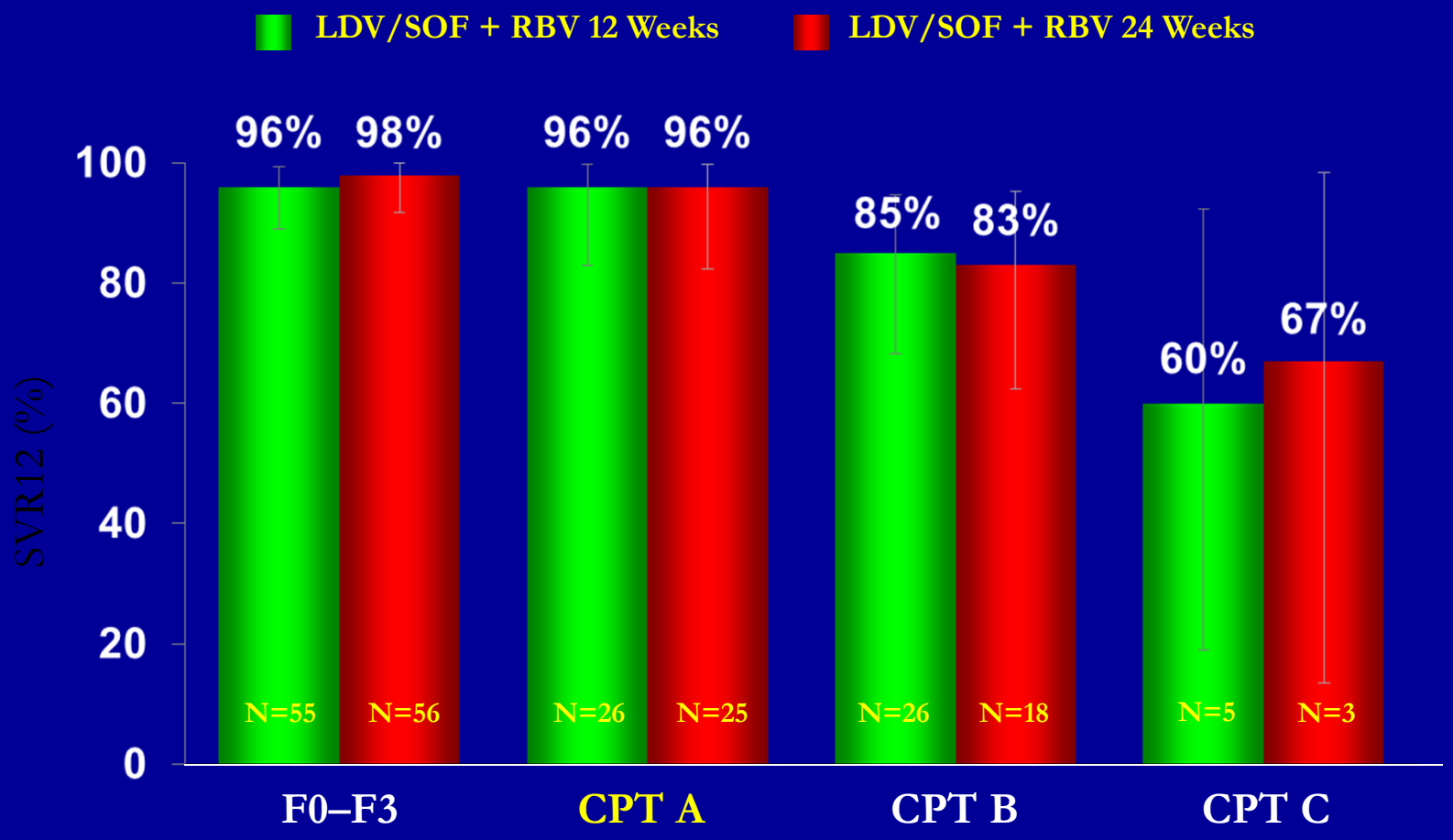
Author, year, (number of patients)	Design	Treatment	Eligibility (%)	Weeks from LT	Follow-up (days)	D/C (%)	SVR (%)	Rejection (%)	Histologic benefit
Sheiner, 1998 [80] (n = 30 versus 41)	Controlled randomized	Interferon-α 3 MU × 3 (12 months) versus placebo	83	2	669 ± 228 594 ± 254	30	0 0	57 56	Yes
Singh, 1998 [81] (n = 12 versus 12)	Controlled randomized	Interferon-α 3 MU × 3 (6 months) versus placebo	73	2	874 (362–1349)	0	0 0	50 42	No
Mazzaferro, 2001 [82] (n = 36)	Uncontrolled, nonrandomized	Inferferon-α 3 MU × 3 + RBV 10 mg/kg per day (12 months)	100	3	1560	0	33	0	Yes
Sugawara, 2004 [47] (n = 23 LDLT)	Uncontrolled, nonrandomized	Inferferon 3–6 MU × 3 + RBV 400–600 mg per day (12 months post HCV RNA -)	100	4.3	780	29	43	33	Yes
Chasalani, 2005 [46] (n = 26 versus 28)	Controlled randomized	Peginterferonalfa-2a versus placebo	NA	3	540	31 32	8 0	12 21	Yes
Shergill, 2005 [48] (n = 22 versus 22)	Uncontrolled, randomized	Interferon-α or peginterferon versus interferon/ peginterferon + RBV	41	2–6	504	47 50	4.5 18	41	NA

Abbreviations: D/C, discontinuation; HCV RNA -, HCV RNA negativity; NA, not available.

Watt K, Veldt B, Charlton M A Practical Guide to the Management of HCV Infection Following Liver Transplantation. American Journal of Transplantation 2009; 9: 1707–1713

Sofosbuvir/Ledipasvir + RBV

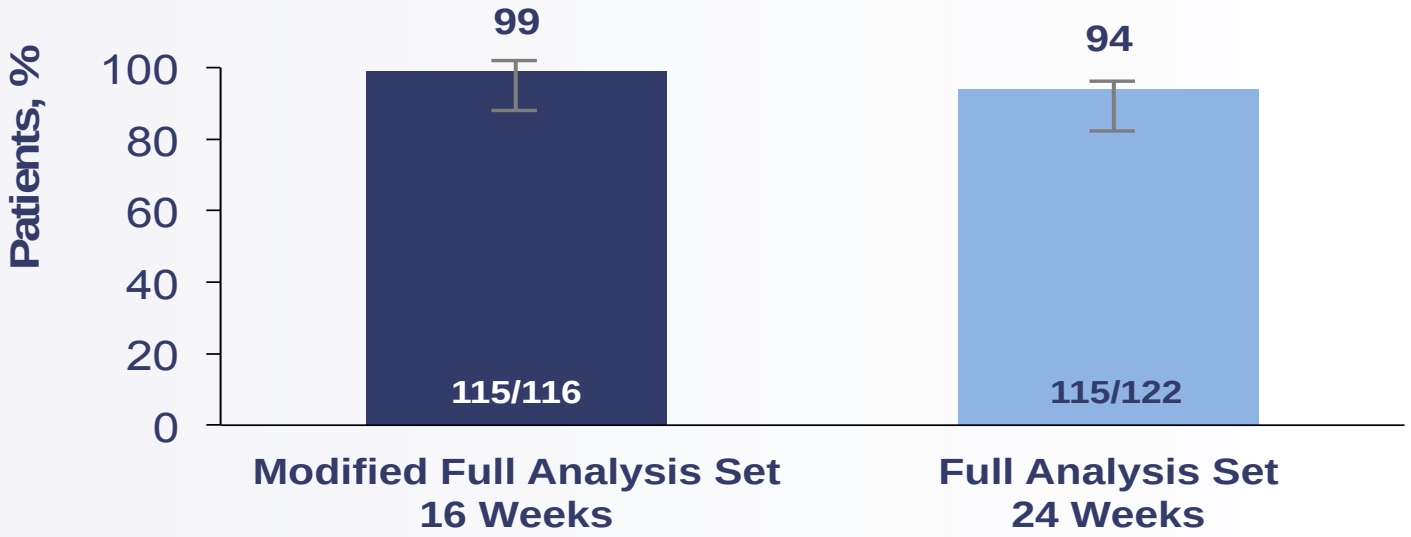
SOLAR-1- Genotype 1, post-transplant HCV recurrence



- Source: Reddy KR, al. 65th AASLD. 2014: Abstract 8.

MK-5172 + MK- 8742

SVR12: GZR/EBR for 12 Weeks in GT1 Patients With Chronic Kidney Disease



Relapse	1[a]		1
Discontinued unrelated to treatment	0		6[b]

[a]Noncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FW12.
[b]Lost to follow-up (n = 2), n = 1 each for death, noncompliance, withdrawal by subject, and withdrawal by physician (owing to violent behavior).

- GZR/EBR was generally safe and well tolerated.

HIV+HCV Coinfection
NIAID ERADICATE Trial - Sofosbuvir-Ledipasvir in GT1

HCV RNA < LLOQ, %	ARV Untreated (n=13)	ARV Treated (n=37)
Week 4	100 (n =13)	100 (n=37)
Week 8	100 (n =13)	100 (n=37)
Week 12 (EOT)	100 (n =13)	100 (n=37)
SVR 4	100 (n =13)	97 (n=36)
SVR 8	100 (n =13)	97 (n=36)
SVR 12	100 (n =13)	97 (n=36)

- Source: Osinusi A, et al. 65th AASLD. 2014: Abstract 84.

Our experience - UIHC LIVER CENTER

Sofosbuvir + Simeprevir

37 patients - HCV recurrence post-transplant

31 geno 1 - sofosbuvir 400 mg +simeprevir 150 mg

3 geno 2 sofosbuvir 400 mg and ribavirin 400 mg

3 geno 3 sofosbuvir 400 mg and ribavirin 400 mg

Our experience - UIHC LIVER CENTER

12/37 patients - cirrhosis post-transplant

Immunosupression – calcineurin inhibitor

32/37 patients – HCV treatment experienced

Our experience - UIHC Liver Center

Sofosbuvir + Simeprevir for post LT HCV

34 patients – achieved SVR 12

3 genotype 1 - relapsers (all cirrhotic)

Well tolerated

No dose changes on immunosuppression

No rejection

BACK TO OUR PATIENT

Clinical Scenario

Post LT patient with fibrosing cholestatic hepatitis C.

Liver failure, renal failure, respiratory failure.

Serum HCV-RNA level was 7.95 log IU/mL.

In view of her life threatening condition

IRB approval - compassionate use of hep C treatment

Clinical Scenario

Combination of sofosbuvir and ribavirin

Reduced doses due to severe renal impairment

Sofosbuvir - 100 mg daily based on pharmacokinetics

Dose increased to 200 mg after 1 week

Full dose sofosbuvir(400 mg daily) after 2 weeks

Clinical Scenario

Ribavirin started at 200 mg once a week

Increased to 200 mg daily 2 weeks later

As renal function improved, ribavirin to 400mg daily and 800 mg daily (after 4 weeks).

HCV RNA viral load decreased > 1 log at 2 weeks

HCV RNA viral load undetectable at 12 weeks

Clinical Scenario

Kidney function improved, normal baseline at 8 weeks

Liver chemistry tests normalized after 8 weeks.

Patient was discharged to rehab after 4 weeks

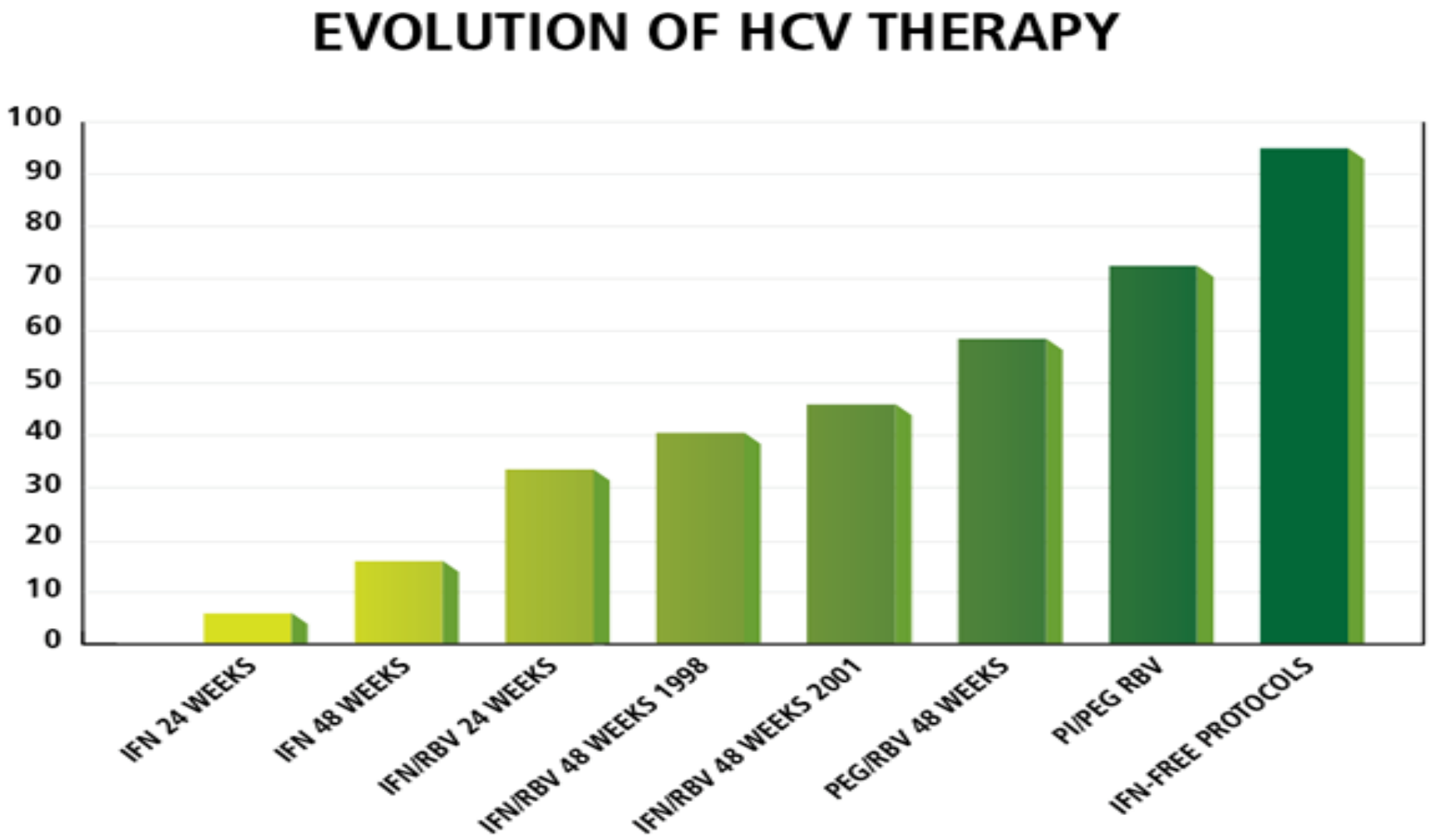
Complete resolution of her multi-organ dysfunction

Patient completed 24 weeks of therapy

Achieved sustained virologic response

The Good !!!

Therapeutic options - Hepatitis C treatment in 2016



Therapeutic options - Hepatitis C treatment in 2016

Regimen		Treatment Naïve	Treatment Experienced	Treatment-Naïve Cirrhosis	Treatment-Experienced Cirrhosis
Daclatasvir + Asunaprevir	Japan GT1b	87%+	81%	N/A	N/A
	Global GT1b	90%	82%		
Daclatasvir + sofosbuvir ± ribavirin	GT1a	96%	97%	-	-
	GT1b	100%	100%	-	-
	GT2	92%*	-	-	-
	GT3	90%	86%	58%	69%
Ledipasvir/sofosbuvir	GT1	-	-	94%	100%
	GT1a	98%	95%	-	-
	GT1b	100%	87%	-	-
Paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin	GT1	-	-	94%*	92%*
	GT1a	97%	96%	-	-
	GT1b	100%	100%	-	-
Simeprevir + sofosbuvir	GT1	94%	-	100%*	93%*
	GT1a	-	89%	-	-
	GT1b	-	94%	-	-
Sofosbuvir + ribavirin	GT1	-	-	60%*	-
	GT1a	82%*	-	-	-
	GT1b	54%*	-	-	-
	GT2	95%	86%	86%	72%
	GT3	93%*	77%*	92%*	60%*

[+]Interferon ineligible/intolerant;

*24 weeks of treatment; GT1 (a/b), genotype-1; GT2, genotype-2; GT3, genotype-3; N/A, not available

doi:10.1371/journal.ppat.1004854.t002

Trial	Population	Study Groups and Duration (Number of Subjects Treated)
C-EDGE TN (double-blind)	GT 1, 4 TN with or without cirrhosis	• ZEPATIER for 12 weeks (N=306) • Placebo for 12 weeks (N=102)
C-EDGE COINFECTION (open-label)	GT 1, 4 TN with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 weeks (N=217)
C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Severe Renal Impairment including Hemodialysis	• EBR* + GZR* for 12 weeks (N=122) • Placebo for 12 weeks (N=113)
C-SCAPE (open-label)	GT 4 TN without cirrhosis	• EBR* + GZR* for 12 weeks (N=10) • EBR* + GZR* + RBV for 12 weeks (N=10)
C-EDGE TE (open-label)	GT 1, 4 TE with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 or 16 weeks (N=105, and 101, respectively) • ZEPATIER + RBV for 12 or 16 weeks (N=104 and 104, respectively)
C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen† with or without cirrhosis	• EBR* + GZR* + RBV for 12 weeks (N=79)

GT = Genotype
TN = Treatment-Naïve
TE = Treatment-Experienced (failed prior treatment with interferon [IFN] or peginterferon alfa [PegIFN] with or without ribavirin [RBV] or were intolerant to prior therapy).
*EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR + GZR = co-administered as single agents.
† Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with PegIFN + RBV.

The Bad !

Drug Interactions - Sofosbuvir & Amiodarone

Drug safety Update – August 15

Simeprevir with sofosbuvir (used for hepatitis C): risk of severe bradycardia and heart block when taken with amiodarone

- concomitant use should be avoided unless other antiarrhythmics cannot be given due to a risk of severe bradycardia and heart block if taken together.
- Extension on previous advice on some combination therapies for hepatitis C.

Viekira Pak -Risk of Liver Failure in Cirrhosis

FDA Adverse Event Reporting System (FAERS)

Viekira Pak - 26 cases of hepatic decompensation and liver failure in patients with underlying cirrhosis.

Some events resulted in liver transplantation or death.

Liver injury occurred within 1-4 weeks of treatment.

The Ugly !

Estimated Medication Cost for Treatment of Genotype 1 Chronic HCV	
Regimen* and Duration	**Regimen Cost**
Daclatasvir + Sofosbuvir x 12 weeks	$147,000
Daclatasvir + Sofosbuvir x 24 weeks	$294,000
Ledipasvir-Sofosbuvir x 8 weeks	$63,000
Ledipasvir-Sofosbuvir x 12 weeks	$94,500
Ledipasvir-Sofosbuvir x 24 weeks	$189,000
Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir x 12 weeks	$84,000
Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir x 24 weeks	$168,000
Sofosbuvir + Simeprevir x 12 weeks	$150,000
Sofosbuvir + Simeprevir x 24 weeks	$300,000

Note: for regimens that include ribavirin add approximately $500 for 12 weeks and $1000 for 24 weeks

Summary

New generation DAA – IFN-free combination

Rapid evolution – new therapies SVR > 95 %

Expand pool of tx candidates (cirrhosis, ESRD)

Referrals - potential to erradicate hepatitis C

Updates - www.hcvguidelines.org